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Name: Diana Hamlet-Kung
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :
Wolfgang R. Streber et al. : Group Art Unit: 1812
Serial No.: 07/322,604 : Examiner: J. Ulm
Filed: March 10, 1989 :
For: **MICROORGANISMS AND PLASMIDS FOR 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D) MONOOXYGENASE FORMATION AND PROCESS FOR THE PRODUCTION OF THESE PLASMIDS AND STRAINS**

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

SIR:

I, Dr. Wolfgang R. Streber being duly warned, declare that:

I am a citizen of Germany, residing at Bartningallee 24, W-1000 Berlin 21, Germany.

I possess the degree of Dr. rer. nat. in Pharmacy , having studied at Ludwig-Maximilians-Universität in Munich.

Since March 1987 I have been employed as a scientist in the Agrochemicals Biotechnology Department of Schering Aktiengesellschaft, Berlin, Germany.

My expertise is demonstrated by my curriculum vitae, which is attached.

I have read and understood the references cited by the Examiner in the Office Action dated November 26, 1991 in the above-identified patent application. I have also read and understood the above-identified patent application.

A person having ordinary skill in the art of plant molecular biology would not find that these references render the claimed

invention obvious. This conclusion is based upon the following facts and observations:

1. Insofar as the inventors are aware, as of the August 29, 1986, priority date of this application, there had been no publication of any results regarding the expression of either a bacterial monooxygenase or any other comparable enzyme in plants. The only type of bacterial enzyme which had been expressed in the plants at the time were enzymes for which either an equivalent enzyme, e.g. EPSP-synthase (Comai et al.), or an essential factor, e.g. ATP for Neomycinphosphotransferase, or both were naturally present in the plants.

The Comai et al. reference therefore discloses the insertion of a very different bacterial enzyme with an endogenous homolog into a plant, as compared with the completely exogenous bacterial gene inserted in the present invention.
EPSP synthase is a protein which is **normally** present in the plant, is necessary for the viability of the plant and is poisoned by the herbicide glyphosate. Comai et al. merely inserted an **additional** copy of a gene coding for that necessary protein which was derived from a glyphosate-resistant bacterium.

In contrast, the present invention provides for the first time a 2,4-D monooxygenase gene and protein in plants, which do not normally possess such an activity. This enzyme posesses a highly unique biological activity. There was no way to predict from this reference, either alone or in combination with the other cited reference, whether:

a) the bacterial 2,4-D monooxygenase could be expressed inside eukaryotic cells, e.g., plant cells, and
b) even if it were, if the biological activity of the 2,4-D monooxygenase would be retained, and,
c) even if it were, if it would be retained at a level compatible with both
    i) the biological activity of herbicide-resistance and
    ii) the viability of the plant.

In particular, at the time the invention was made, there were no references disclosing the identification of the

biological activity of 2,4-D monooxygenase outside of living bacterial cells. In fact, the Amy et al. reference only shows the 2,4-D monooxygenase enzymatic activity in E. coli cells. It was not known whether there were additional factors present (or absent) inside bacterial cells the presence (or absence) of which were required for enzymatic activity.

2. 2,4-dichlorophenol, which is produced by 2,4-D monooxygenase from 2,4-dichlorophenoxy acetic acid (2,4-D), is known to be toxic to the respiration of living cells. At the time the invention was made, therefore, it would not have been obvious whether in the presence of a 2,4-D monooxygenase gene the plants would be protected from the toxicity of the reaction product 2,4-dichlorophenol, as well as from the toxicity of the 2,4-D itself, or if in fact, this reaction product would itself cause damage.

Therefore, in view of the differences in the enzymes, in particular the endogenous versus exogenous nature of the enzymes, the very different chemistry of the herbicides, the metabolic pathways affected, the toxicity of reaction products, etc., between the reference and the present invention, a skilled worker would not be able to predict anything from the cited references, particularly in view of Comai, with respect to the present invention.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the applciation or any patent issuing thereon.

3. April 1992 — W. Freber

Date

CURRICULUM VITAE

name:	Dr. Wolfgang R. Streber
date and place of birth:	24. Feb. 1958 in Munich, Germany

Education and Scientific Qualification:

1964 - 1977	school in Munich
Nov. 1977 - Oct. 1982	studies in pharmacy at the Ludwig-Maximilians-Universität (LMU) in Munich
Dec. 1982	awarded "Approbation" (degree) in pharmacy
Jan. 1983 - Feb. 1987	scientific work for doctoral dissertation in the group of Prof. Dr. M. H. Zenk at the Institute of Pharmaceutical Biology of the LMU about the bacterial metabolism of the herbicide 2,4-D
Feb. 1987	awarded doctorate in the faculty of Chemistry and Pharmacy (LMU)
since March 1987	employment as a scientist in the Agrochemicals Biotechnology Department of the Schering AG, Berlin

W. Streber